REMARKS

The Office action reiterated the telephonic restriction and resulting election of species, with traverse, for the examination of a compound of formula I* wherein X^1 is N, X^2 an X^3 are CH; R^2 is optionally substituted phenyl, and R^1 is H; R^{3*} is $-C(O)NZ^{5*}Z^{6*}$ wherein Z^{5*} an Z^{6*} together with the nitrogen atom to which they are attached form a heterocyclic ring (substituted); R^4 is methyl; and R^5 is H.

The Office action noted that when a search was conducted based on the elected species prior art was found, and therefore the Markush-type claims (claims 61 et seq.) were only examined to the extent of the searched subgenus. Applicants submit that since the prior art does not anticipate or otherwise teach or suggest the compounds of formula I* for treating or preventing atrial fibrillation as is claimed, the scope of the defined subgenus may be extended. Accordingly, it is requested that the scope of the examination and any claim allowance be extended to include compounds of formula I*, and the various claimed uses thereof, in which R^1 is $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2-$ as originally defined, but other than H or hetero; R^2 and R^5 are each $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2-$ as originally defined, but other than hetero; and R^4 is alkyl or substituted alkyl as originally defined.

Applicants reserve the right to continue prosecution of all non-elected subject matter in one or more divisional applications.

The Rejection under 35 U.S.C. δ112, First Paragraph

Claims 69-79 were rejected under 35 U.S.C. §112, first paragraph for the stated reason that "the specification, while being enabling for the treatment of atrial arrhythymias, does not reasonably provide enablement for the treatment of all other diseases of the instant claims." The rejection iterates several statements in consideration of the *Wands* factors toward this finding, which are addressed below.

First, the rejection notes that the use disclosed in the specification is as inhibitors of Kv1 subfamily of voltage-gated K+ channels useful in the treatment of a wide variety of diseases. The reference to standard assays in Applicants' specification is noted, however the Examiner goes on to state that this area of receptor interactions (potassium channel) are "highly structure specific and unpredictable," citing an article by Yi et al. for the proposition that "more questions need to be

answered to better understand the different functions" and "much remains to be done to determine the general themes" of potassium channels. Next, the Examiner states that there is no nexus provided to correlate the potassium channel inhibitory activity with treatment of the disorders recited in the instant claims.

The compounds suitable for achieving the therapeutic effects claimed herein act as inhibitors of the K_v1 subfamily of voltage gated K^+ channels, which includes the $K_v1.5$ subfamily that has been linked to the ultra-rapidly activating delayed rectifier current, also known as I_{KUR}. According to the literature,

- Inhibitors of $K_v1.5$ and other $K_v1.x$ channels stimulate gastrointestinal motility. See, Frey et al., "Blocking of cloned and native delayed rectifier K channels from visceral smooth muscles by phencyclidine," Neurogastroenterol Motil. 2000 Dec;12(6):509-16; Hatton et al., "Functional and molecular expression of a voltage-dependent K(+) channel (Kv1.1) in interstitial cells of Cajal," J Physiol. 2001 Jun 1;533 (Pt 2):315-27; Vianna-Jorge et al., "Shaker-type Kv1 channel blockers increase the peristaltic activity of guinea-pig ileum by stimulating acetylcholine and tachykinins release by the enteric nervous system," Br J Pharmacol. 2003 Jan; 138(1):57-62; Koh et al., "Contribution of delayed rectifier potassium currents to the electrical activity of murine colonic smooth muscle," J Physiol. 1999 Mar 1; 515 (Pt 2):475-87.

- Inhibitors of Kv1.5 relax pulmonary artery smooth muscle. Thus, the compounds of the invention would be useful in treating hypertension and other vascular diseases. See, Davies et al., "Kv channel subunit expression in rat pulmonary arteries," Lung. 2001;179(3):147-61. Epub 2002 Feb 04; Pozeg et al., "In vivo gene transfer of the O_2-sensitive potassium channel Kv1.5 reduces pulmonary hypertension and restores hypoxic pulmonary vasoconstriction in chronically hypoxic rats," Circulation. 2003 Apr 22;107(15):2037-44. Epub 2003 Apr 14.

- Inhibitors of Kv1.3 increase insulin sensitivity. Hence, the compounds of the invention would be expected to be useful in treating diabetes. See, Xu et al., "The voltage-gated potassium channel Kv1.3 regulates peripheral insulin sensitivity," Proc Natl Acad Sci U S A. 2004 Mar 2;101(9):3112-7. Epub 2004 Feb 23 (epublished 2004 Feb 23); MacDonald et al., "Members of the Kv1 and Kv2 voltage-dependent K(+) channel families regulate insulin secretion," Mol Endocrinol. 2001 Aug;15(8):1423-35; MacDonald et al., "Voltage-dependent K(+) channels in pancreatic beta cells: role, regulation and potential as therapeutic targets," Diabetologia. 2003 Aug;46(8):1046-62. Epub 2003 Jun 27.

- Stimulation of Kv1.1 is believed to reduce seizure activity by hyperpolarizing neurons. Thus, the compounds of the invention are believed to be useful in treating seizures, including seizures associated with epilepsy and other neurological diseases. See, Rho et al., "Developmental seizure susceptibility of kv1.1 potassium channel knockout mice," Dev Neurosci. 1999 Nov;21(3-5):320-7; Coleman et al., "Subunit composition of Kv1 channels in human CNS," J Neurochem. 1999 Aug;73(2):849-58; Lopantsev et al., "Hyperexcitability of CA3 pyramidal cells in mice lacking the potassium channel subunit Kv1.1," Epilepsia. 2003 Dec;44(12):1506-12; Wickenden, "Potassium channels as anti-epileptic drug targets," Neuropharmacology. 2002 Dec;43(7):1055-60.

- Inhibition of Kv1.x channels improves cognition in animal models. Thus, the compounds of the invention are believed to be useful in improving cognition and/or treating cognitive disorders. See, Cochran et al., "Regionally selective alterations in local cerebral glucose utilization evoked by charybdotoxin, a blocker of central voltage-activated K+-channels," Eur J Neurosci. 2001 Nov;14(9):1455-63; Kourrich et al., "Kaliotoxin, a Kv1.1 and Kv1.3 channel blocker, improves associative learning in rats," Behav Brain Res. 2001 Apr 8;120(1):35-46.

Copies of the cited references, to the extent not previously submitted, are presented in the accompanying Information Disclosure Statement.

The rejection further states that there is no reasonable basis for assuming that the claimed compounds will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent. It is not sure what is intended by this statement, as it is Applicants' understanding that the restriction issued in this application was for the purpose of separating compounds with structural commonalities, by classification, for the purpose of effective examination. If this was not the intent, further clarification is respectfully requested.

On the basis of the foregoing remarks, withdrawal of the rejections on the stated grounds is respectfully requested.

The Rejection under 35 U.S.C. δ112, Second Paragraph

Claims 81-82 were rejected under 35 U.S.C. δ112, second paragraph, as being indefinite because the terms "pyrimidine" and "pyrazolo" were hyphenated in claim 81. These minor typographical errors have been corrected in the instant amendment.

The Rejection under 35 U.S.C. δ102

Claims 61-63 and 66-69 were rejected as being anticipated by European Patent EP 0217142 (Tsuda). The rejection states that the claimed method of treating arrhythmia reads on the method of use taught for the referenced compounds. Applicants respectfully traverse.

Applicants' presently claimed compounds differ from the Tsuda compounds listed in the patent specification and therefore are not anticipated by that any example in that disclosure. In Applicants' compounds of formula I*, R^7 (corresponding to Tsuda's $R^{8(2)}$) are not H, Me, cyclopentyl or F when R^{3*} (corresponding to Tsuda's R^1) is an ester. Withdrawal of this rejection is requested.

The Rejection under 35 U.S.C. 103

Claims 61-63, 66-69 and 81-83 were also requested as being unpatentable over Tsuda, allegedly because it would have been obvious to "select any of the species taught by the reference ... [and] one of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been selected by the reference as a whole." It is also stated that the combination of Applicants' claim 83 would have been obvious because the additional agents would be known to one skilled in the art. Applicants traverse.

As pointed out above, the compounds defined by the present claims do not fall within the scope of Tsuda's disclosure. Tsuda lists over 800 compounds that are different from the compounds of the present invention. There is no teaching or suggestion for further experimentation to derive the claimed compounds. An obvious to try rationale, which seems to be the suggestion of the rejection, is not a proper basis for rejection of Applicants' claims. Therefore, withdrawal of this rejection is respectfully requested.

The Double Patenting Rejection

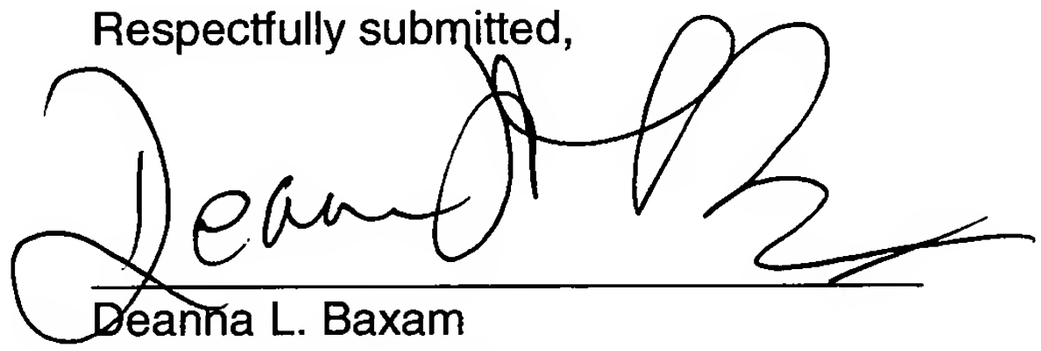
Claims 61-63, 66-69 and 81-83 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of commonly owned and assigned U.S. Patent 6,706,720. The rejection states that although the conflicting claims are not identical. It is also stated that the allegedly conflicting claims are not patentably distinct from each other because

- there is no patentable distinction;
- the present claims have a genus that overlaps the genus claimed in the reference
- it would have been obvious to one or ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and thus the same use as taught for the genus as a whole, i.e. pharmaceutical agents.

Applicants respectfully traverse. First, it is pointed out that this application is filed as a divisional application (resulting from a restriction requirement imposed by the Office) of the application which matured into U.S. Patent 6,706,720. As a matter of law therefore, imposition of a double patenting rejection of this type is improper. Neither is there any real issue of overlap between the claims of this application and those of the patent, because the genus of compounds defined in the present claims do not overlap with the compounds claimed in the granted patent.

Please charge any necessary additional fees associated with this filing or credit any overpayment to Deposit Account No. 19-3880.

Respectfully submitted,



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